

Complete Summary

GUIDELINE TITLE

Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder. London (UK): National Institute for Clinical Excellence (NICE); 2003 Sep. 26 p. (Technology appraisal; no. 66).

GUIDELINE STATUS

This is the current release of the guideline.

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SCOPE

DISEASE/CONDITION(S)

Acute mania associated with bipolar I disorder

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
 Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Psychiatry
Psychology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical and cost-effectiveness of olanzapine and valproate semisodium in the treatment of mania associated with bipolar disorder

TARGET POPULATION

Adults with acute mania associated with bipolar I disorder

INTERVENTIONS AND PRACTICES CONSIDERED

1. Olanzapine
2. Valproate semisodium

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
 - Response rate
 - Suicide
 - Hospitalisation rate
 - Side effects of treatment
 - Quality of life
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology

considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the National Health Service (NHS) Centre for Reviews and Dissemination/Centre for Health Economics, University of York. (See the "Companion Documents" field.)

Search Strategy

The literature search was not limited to any specific study design, and thus the searches were conducted without methodological filters, and consisted of terms for the drug interventions combined with terms for bipolar disorder. Full details of the search strategies for this review are presented in Appendix 1 of the Assessment Report (see "Availability of Companion Documents" field).

The following databases were searched for relevant published literature: Biosis, Cochrane Controlled Trials Register (CCTR), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Health Economic Evaluations Databases (HEED), LILACS, MEDLINE, National Research Register (NRR), NHS Economic Evaluation Database (NHS EED), PsycINFO, and Science Citation Index.

Searches were also carried out on the Internet using the medical search engine OMNI (<http://omni.ac.uk/>), meta-search engine Copernic (<http://www.copernic.com/>), and general search engines Alta Vista (<http://www.altavista.com/>) and Google (<http://www.google.com/>). Specialist Mental Health related web sites were also searched; The Royal College of Psychiatrists (<http://www.rcpsych.ac.uk/>), the American Psychiatric Association (<http://www.psych.org/index.cfm>), and The National Institute of Mental Health (<http://www.nimh.nih.gov/>).

In addition the bibliographies of retrieved articles and industry submissions made to the National Institute for Clinical Excellence (NICE) were searched for further relevant studies.

Inclusion and Exclusion Criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of potentially relevant titles and abstracts were obtained where possible and the relevance of each study assessed according to the criteria below. Studies that did not fulfill all of the criteria were excluded and their bibliographic details listed with the reason for exclusion (see Appendix 2 of the Assessment Report [see "Availability of Companion Documents" field]). Any discrepancies were resolved by consensus and if necessary a third reviewer was consulted.

Study Design

The following study designs were included:

- Randomised controlled trials (RCTs) where olanzapine, quetiapine, or valproate semisodium were used either as mono or adjunctive therapy for the treatment of an acute manic episode. Acute mania was taken to mean any duration of mania reported in the studies up to a maximum of 10 weeks. The most commonly reported duration of RCTs was 3 weeks; therefore if a study

- reported data at 3 weeks and other time points, we extracted the 3 week data only.
- A broader range of studies were considered in the assessment of cost effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options, and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses), were included.

Interventions

Olanzapine, quetiapine, or valproate semisodium used either as mono or adjunctive therapy within their licensed indications for the treatment of an acute manic episode, though quetiapine is not currently licensed for treatment of mania associated with bipolar affective disorder. Comparators were any agents used for the treatment of an acute manic episode.

Participants

Individuals with bipolar affective disorder who are experiencing an acute manic episode.

Outcomes

Data on the following outcome measures were included:

- Response (e.g., measured by rating scales)
- Suicide
- Rates of hospitalisation/discharge/length of hospital stay
- Adverse effects (e.g., gastrointestinal disturbances, weight gain, and extrapyramidal side effects [EPS])
- Costs from all reported perspectives
- Quality of life and personal preference, where reported
- Attrition/leaving the study early

NUMBER OF SOURCE DOCUMENTS

Eighteen randomised trials met the inclusion criteria.

Two studies identified in the systematic review met the criteria for inclusion in the cost effectiveness review. In addition to these two studies, supplementary economic evidence was submitted by two of the stakeholders (Sanofi-Synthelabo Ltd and Eli Lilly).

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the National Health Service (NHS) Centre for Reviews and Dissemination/Centre for Health Economics, University of York. (See the "Companion Documents" field.)

Data Extraction Strategy

Data relating to study details and quality (see Appendix 3 and 4 of the Assessment Report [see "Availability of Companion Documents" field]) were extracted by one reviewer into an Access database and independently checked for accuracy by a second reviewer. Disagreements were resolved through discussion and, if necessary, a third reviewer was consulted. Data from studies with multiple publications were extracted and reported as a single study. Where possible, people who left the study early were added back in to dichotomous outcomes as having had the "bad" outcome (e.g., for the outcome "response," missing persons were assumed to be nonresponders). A sensitivity analysis was carried out to assess whether including these people as having had the "good" outcome made a substantial difference to the results. However this worst-case intention to treat (ITT) analysis was not possible for the majority of people who left the included studies early, as they had already been added back in by the trial authors using the last observation carried forward (LOCF) method and data reported for the group as a whole. The reviewers could not therefore separate the endpoint data of people who completed the trial from the LOCF data of people who left the trial early.

Quality Assessment Strategy

The quality of the individual studies was assessed by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus and, if necessary, a third reviewer was consulted. The quality of clinical effectiveness studies was assessed using criteria based on CRD Report No. 423 (Appendix 4 of the Assessment Report [see "Availability of Companion Documents" field]). The quality of the cost-effectiveness studies was assessed using a checklist updated from that developed by Drummond et al. (see Appendix 5 of the Assessment Report [see "Availability of Companion Documents" field]).

This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Clinical Excellence.

Methods of Analysis/Synthesis

Details of the extracted data and quality assessment for each individual study of clinical effectiveness were presented in structured tables and as a narrative description. The possible effects of study quality on the effectiveness data and review findings were examined. Where sufficient data were available, treatment effects were presented in the form of relative risks (RR) or mean differences (for continuous data) as appropriate. Relative risk and mean difference data were presented as Forest plots but only pooled where this made sense clinically and statistically. Heterogeneity between studies was assessed by considering differences in (a) study population, (b) intervention, (c) outcome measures and (d) study quality. Studies were grouped by drug and, within each drug, by comparator used. We treated missing persons as nonresponders as the base-case scenario. Where possible we carried out a sensitivity analysis using positive assumptions instead for missing persons. Chi square tests of heterogeneity were performed for the outcomes if pooling was indicated.

Methods of Analysis for Economic Studies

Details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables. This covered studies based on patient-level data and decision models and included any studies provided by manufacturers.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Details of each identified published economic evaluation, together with a critical appraisal of its quality were presented in structured tables. This covered studies based on patient-level data and decision models and included any studies provided by manufacturers.

The review of the economic evidence from the literature and stakeholder submissions highlighted a number of significant limitations in existing studies assessing the cost-effectiveness of alternative drugs for the acute manic episode in bipolar disorder.

These limitations meant that it was not possible to make a reliable comparison of the relative cost-effectiveness of the alternative drugs on the basis of existing evaluations in the context of the National Health Service (NHS). To overcome these limitations and to assist the decision making process in the context of the

NHS, a new model was developed. The model is used to provide an estimate of the cost-effectiveness of the alternative drugs when used as part of treatment for the acute manic episode only.

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Olanzapine and valproate semisodium, within their licensed indications, are recommended as options for control of the acute symptoms associated with the manic phase of bipolar I disorder.
- Of the drugs available for the treatment of acute mania, the choice of which to prescribe should be made jointly by the individual and the clinician(s) responsible for treatment. The choice should be based on an informed discussion of the relative benefits and side-effect profiles of each drug, and should take into account the needs of the individual and the particular clinical situation.
- In all situations where informed discussion is not possible advance directives should be taken fully into account and the individual's advocate and/or carer should be consulted when appropriate.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of olanzapine and valproate semisodium in the treatment of adults with mania associated with bipolar disorder

POTENTIAL HARMS

- The Summary of Product Characteristics states that weight gain and somnolence are very common side effects of olanzapine. Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases, and therefore appropriate clinical monitoring is advisable in people with diabetes or with risk factors for the development of diabetes mellitus. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- The Summary of Product Characteristics states that valproate semi-sodium very commonly causes weight gain, which may be marked and progressive. Severe, sometimes fatal, liver damage has exceptionally been reported. Liver function should be assessed before therapy and during the first 6 months; tests that reflect protein synthesis, particularly prothrombin time, are most relevant. Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are therefore recommended.

For full details of side effects, precautions, and contraindications, see the Summary of Product Characteristics, available at <http://emc.medicines.org.uk/>.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Olanzapine: Contraindications include angle-closure glaucoma and breast-feeding.
- Valproate: Contraindications include hypersensitivity to active substance or excipients, active liver disease, personal or family history of severe hepatic dysfunction, and porphyria.

For full details of side effects, precautions, and contraindications, see the Summary of Product Characteristics, available at <http://emc.medicines.org.uk/>.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement.

The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

- At the date of issue of this guidance, within the classes of agents referred to the Institute by the Department of Health and the Welsh Assembly Government only olanzapine and valproate semisodium held a marketing authorisation for the treatment of acute mania in bipolar I disorder.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- Clinicians with responsibility for treating people with bipolar I disorder should review their current practice and policies to take account of the guidance (see the "Major Recommendations" field).
- Local guidelines, protocols or care pathways that refer to the care of people with bipolar I disorder should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
 - Olanzapine and valproate semi sodium (VSS) are considered as options for the control of the acute symptoms associated with the manic phase of bipolar I disorder.
 - The individual and the clinician(s) responsible for treatment decide jointly on which of the available drugs for the treatment of acute mania to use, after an informed discussion about the relative benefits and the side-effect profiles of each drug and taking into account the needs of the individual and the particular clinical situation.
 - When making the choice of which of the available drugs to use, in all situations where informed discussion is not possible, any advance directive is fully taken into account and the individual's advocate and/or carer is consulted when appropriate.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

Foreign Language Translations

Patient Resources

Quick Reference Guides/Physician Guides

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder. London (UK): National Institute for Clinical Excellence (NICE); 2003 Sep. 26 p. (Technology appraisal; no. 66).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Sep

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder. Summary. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 Sep. 2 p. (Technology appraisal 66). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- A rapid and systematic review of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. Assessment report. NHS R&D HTA Programme; 2003 Apr 3. 281 p. Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0289. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the [original guideline document](#).

PATIENT RESOURCES

The following is available:

- The use of olanzapine and valproate semisodium to treat acute mania associated with bipolar I disorder. Understanding NICE guidance – information for people with bipolar I disorder, their advocates and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 Sep. 9 p. (Technology appraisal 66).

Electronic copies: Available in English and Welsh in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](http://www.nice.org.uk).

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0290. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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